UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/678,723	10/02/2003	Eduardo Marban	001107.00459	6122

22907 7590 03/05/2009
BANNER & WITCOFF, LTD.
1100 13th STREET, N.W.
SUITE 1200
WASHINGTON, DC 20005-4051

EXAMINER	
MONTANARI, DAVID A	
ART UNIT	**PAPER NUMBER**
1632	

MAIL DATE	DELIVERY MODE
03/05/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	**Application No.** 10/678,723	**Applicant(s)** MARBAN ET AL.	
	Examiner David Montanari	**Art Unit** 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 December 2008*.
2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.
3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6,20-34,42,46-48 and 77-82* is/are pending in the application.
4a) Of the above claim(s) _____ is/are withdrawn from consideration.
5)☐ Claim(s) _____ is/are allowed.
6)☒ Claim(s) *1-4,6,20-34,42,46-48 and 77-82* is/are rejected.
7)☐ Claim(s) _____ is/are objected to.
8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.
10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a)☐ All b)☐ Some * c)☐ None of:
1.☐ Certified copies of the priority documents have been received.
2.☐ Certified copies of the priority documents have been received in Application No. _____.
3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicants arguments and amendments filed on 12/15/2008 have been entered.
2. Claims 1-4, 29, 32-34, 42, 46, 47 and 77-82 are amended.
3. The rejection of claims 1-4, 6, 20-34, 42 and 77-82 under 35 USC 103(a) is withdrawn in view of Applicants amendments to the claims and the new 35 USC 112, first paragraph, enablment rejection below.
4. The rejection of claims 1-4, 6, 20-34, 42 and 77-82 under 35 USC 112, first paragraph, scope of enablment is withdrawn in view of the new 35 USC 112, first paragraph, enablment rejection below.
5. The rejection of claims 29 and 30 under 35 USC 112, second paragraph is withdrawn.
6. Claims 1-4, 6, 20-34, 42, 46-48 and 77-82 are examined in the instant application.

Claim Objections

Claims 1, 46 and 47 are objected to because of the following informalities: each of these claims recites “a pre-determined region of excitable cells of a mammal” in the preamble. However the “of” following the word "cells" should be changed to the word "in". The current wording of the claims suggests that the excitable cells are not in the mammal, but rather are isolated cells. The claimed methods are drawn to in vivo modulation of calcium channels in the excitable cells of specific regions in the mammal. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 6, 20-34, 42, 46-48 and 77-82 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The breadth of the claimed method encompasses modulating the activity of a calcium channel in a pre-determined region of an excitable cell and a nucleic acid that comprises nucleic acid sequences which are not contiguous and in disagreement among themselves.

While the nature of the invention is a method of modulating L-type calcium channels in excitable cells (i.e. neurons and skeletal muscle or any cell that can propagate action potential) having an L-type calcium channel as discussed by Lipscombe D. (2002, Circulation Res., Vol. 90(9), pgs. 981-987 see pg. 981, col. 1 lines 1-3 particularly) and Elliott et al. (2001, Cell Calcium, Vol. 30(2), pgs. 72-93) the claimed method as presently written is non-enabling.

Applicants, through their working examples, have only taught that the full-length GEM WT sequence and the less-effective mutant W269G have exhibited any modulation of calcium channel activity. However the claimed methods encompass any manner of nucleic acid combinations that make up the GEM protein sequence of SEQ ID NO: 1. There is a significant disagreement between steps (a) and (b) of claims 1, 46 and 47 such that the skilled artisan could not predictably practice the claimed method. In each of said methods, a nucleic acid encoding a GEM protein comprising (a) an amino acid sequence at least 99% identical to SEQ ID NO: 1 and (b) a C- or N- terminal deletion of between 1 to 100 amino acids relative to the amino acid sequence of SEQ ID NO: 1 is contacted with excitable cells. However, since the nucleic acid of step (a) is only 99% identical to SEQ ID NO: 1 and step (b) requires C- or N-terminal deletions from 1 to 100 amino acids relative to said 99% amino acid sequence the skilled artisan could conceivably create multitudes of different proteins which may or may not have GEM protein function. This disconnect between steps (a) and (b) is clearly demonstrated in the working examples teaching that an adenovirus comprising a nucleic acid encoding GEM was locally delivered to guinea-pig hearts (Example 1, pg. 41). The specification continues to teach regarding said example that WT GEM expression results in near total inhibition of L-type calcium current, however the less-effective mutant W269G (which has a single amino acid change at position 269) results in a more manageable but still significant inhibition of calcium channel activity (Example 1, pg. 41). Parts (a), (b) and (c) are being interpreted as being in the alternative such that the nucleic acid recited in claims 1, 46 and 47 will comprise one of the limitations recited in each part. This interpretation, also has issues of enablement since (a) and (b) do not recite any functional language for the protein encoded by the nucleic acid. Similarly (c) provides for any variant nucleic acid sequence that will have a decreased affinity for calmodulin in the encoded protein. The skilled artisan could not predictably rely that the protein produced by any of nucleic acids of (a)-(c) acid would modulate the activity of a calcium channel. Further in some working examples the W269G mutant is no different from a negative control and exhibits no calcium channel activity modulation (pg. 44 Example 2 lines 18-20). Compounding this fact is that the WT GEM protein when delivered under certain conditions such as a hypertensive phenotype is lethal to the recipient (pg. 46 lines 30-31, Example 4). The claimed method encompasses using any variant (for the reasons discussed above regarding the limitations set for in (a)-(c)) of the protein encoded by the nucleic acid sequence set forth in SEQ ID NO: 1, including truncated, partial and non-functioning proteins. This is problematic for the skilled artisan since the claimed method is drawn to the in vivo modulation of calcium channel activity. As the specification teaches throughout the working examples (1-5) the full-length wild-type sequence set forth in SEQ ID NO: 1 that encodes the GEM protein is very potent (when overexpressed) in its ability to reduce intracellular calcium by regulating calcium channel activity. In this regard Applicant has used a “weakened” form of the GEM protein, represented by the W269G mutant, to evaluate the ability of the claimed method to modulate calcium channel activity. Since it is disclosed in the specification that using the full-length SEQ ID NO: 1 sequence can be lethal, it is obvious to the skilled artisan that any mutant, truncated, or weakened form of the protein encoded by SEQ ID NO: 1 should be both functional to enable the claimed method but not to the point of killing the subject to be treated. If the subject dies due to a significant reduction in calcium channel activity, then no modulation of calcium channel will effectively occur, it will just be completely shut down upon death. The pending claims, particularly 1, 46 and 47, recite that the full-length sequence set forth in SEQ ID NO: 1 will not be used in the claimed methods, but rather a truncated form based upon the limitation set forth in (a)-(c). However the specification has not taught any form of a truncated protein. The W269G mutant is a single base polymorphism of the GEM protein and is not reflective of the claimed invention. Since the specification has not taught any other nucleic acids other the full-length wild-type GEM protein and the W269G mutant, the skilled artisan cannot rely upon the teachings in the specification to predictably and without and undue amount of experimentation develop and use the nucleic acid recited in claims 1, 46 and 47 such that the methods would be practiced commensurate with their scope.

The specification continues that the delivery of the WT GEM shortened the QT interval (Example 2, pgs. 44), and caused a reduction of heart rate in atrial fibrillation (Example 3, pg. 45) in guinea-pigs as well as attenuation of cardiac hypertrophy (Example 4, pg. 46) in mice. In contrast to the WT GEM, the W269G mutant in this example did not change the QT interval when used under the same conditions. The specification continues to teach that in a swine atrial fibrillation model GEM gene transfer to the swine heart via intracoronary perfusion resulted in prolongation of the PR interval monitored by surface EKG, the AH interval monitored by intracardiac electrogram and caused a 20% reduction in the ventricular rate during atrial fibrillation (pg. 45 Example 3).

However an examination of the working examples as a whole presents a complex picture to the skilled artisan as how to determine the effectiveness the nucleic acid encoding a GEM protein. Each of Examples 1-4 demonstrates a different phenotype situation (that is dependent on calcium channel activity) and in each case the WT GEM protein and the W269G mutant differ in how they impact said phenotypes through calcium channel activity modulation. Further the claims encompass and recite variants in the amino acid sequence of the GEM protein with no definable boundaries since there is a significant disagreement between steps (a) and (b). Collectively the working examples in view of the newly amended claims presents a situation of unpredictability regarding the enabled practice of the claimed method such that the skilled artisan could not predictably modulate the activity of a calcium channel in an excitable cell.

Regarding the use of GEM protein in calcium channel modulation the art also teaches a complex case for using the GEM protein in such a method. For example, Beguin et al. teach that the GTP-bound form of kir/GEM (a Ras-related small G-protein) inhibits high-voltage-activated calcium channel activity by interacting directly with the beta-subunit (pg. 701, Abstract). Beguin continues to teach that inhibition of L-type calcium channels by kir/GEM prevents calcium triggered exocytosis in hormone-secreting cells and propose that kir/GEM interacts with betasubunits regulating calcium channel expression at the cell surface (pg. 701, Abstract, last four lines). Beguin summarizes that kir/GEM could have a protective effect against an overload of calcium (toxicity) that impairs a variety of cellular functions and may also inhibit cell proliferation by reducing calcium-mediated cell growth (pg. 705, col. 1 parag. 1, last four lines). However, while Beguin teaches that using GEM protein could have a protective effect against an overload of calcium, this protective effect is conditional as the working examples summarized above demonstrate. Using WT/full-length/or fully active GEM protein to modulate calcium channel activity is near total in its effectiveness to blockade calcium channel excitement. Applicants have attempted to balance this by using a mutant of the WT GEM protein that is less-effective and less lethal, however this balance is not reflected in the claims. The claims are very broad with respect to what exact GEM protein (based upon amino acid sequence) will be used within the claimed method. Further compounding this issue is that the newly amended claims provide no limits or definition of what amino acid sequence the GEM protein will comprise since there is a significant disagreement with respect to the amino acid makeup of the GEM protein used in said method. All of this leads the skilled artisan to determine that the claimed method is both undue in practice and unpredictable since the sequence of the GEM protein has such a significant impact on the calcium channel modulation in excitable cells to the extent that the sequence may kill the subject or may have no effect at all.

In conclusion, based upon the lack of teaching in the specification regarding the structure of the nucleic acid that will encode for a truncated GEM protein, the pending claim language and the disagreement between (a)-(c), the claimed method is not enabled. The skilled artisan could conceivably use a truncated or mutant form of the protein based upon the limitations in (a)-(c) that results in an even more potent form of the wild-type GEM protein such that all calcium channel activity is completely abolished, which would be render any modulation of calcium channel activity moot.

Claims 1-4, 6, 20-34, 42, 46-48 and 77-82 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

When the claim is analyzed in light of the specification, the instant invention encompasses proteins that share a 99% protein sequence with SEQ ID NO: 1 and further a C- or N-terminal deletion of between from 1 to 100 amino acids relative to the amino acid sequence of SEQ ID NO: 1. The specification teaches (parag. 0137):

> "As discussed, the invention methods can be used with recombinant adenoviruses that encode a mammalian Gem protein or a variant thereof. By "variant" is meant a nucleic acid sequence that encodes protein with at least about 70% sequence identify to the protein sequence shown above as SEQ ID NO. 1, preferably at least about 80%, more preferably at least about 90% or more up to about 99% identical."

In view of this teaching the specification has failed to teach possession of any protein that is less than 100% sequence identical with SEQ ID NO: 1 that exhibits modulation of a calcium channel in a cell. The specification provides no description of any sequence other than SEQ ID NO: 1 that would indicate possession at the time of filing. In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, only SEQ ID NO:1 is sufficiently described to indicate possession of a gene that encodes a product capable of modulating calcium channel activity. The specification does not provide any disclosure as to what the complete structure would be of any gene other than the one disclosed in SEQ ID NO:1. The specification teaches no structural analysis for said gene. Next, then, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (i.e. other than nucleotide sequence), specific features and functional attributes that would distinguish different members of the claimed genus. In the instant case, the only characteristic described, is that the protein represented in SEQ ID NO:1 modulates calcium channel activity. The specification does not teach any other identifying characteristic or any other related sequences that would guide the artisan to contemplate other genes that would be encoded by less than the full sequence represented in SEQ ID NO:1. Further compounding the issue of written description regarding the protein encoded by SEQ ID NO: 1 is that the newly amended claims recite language which provide for a protein that could have not functional or identifying characteristic with SEQ ID NO: 1 such that calcium channel modulation occurs in response to the expression of the protein now recited in the instant claims. The nucleic acid used in the claimed method is interpreted to be in the alternative and comprise the separate and distinct limitations recited in steps (a)-(c), which would encompass protein having the functional property of reduced affinity for calmodulin with no corresponding nucleic acid sequence and nucleic acid sequences without any functional properties. This function of the protein is related to the structure of the nucleic acid, which as stated above, the specification has only disclosed the full-length sequence for in SEQ ID NO: 1. However, the claims are not limited to the full-length nucleotide sequence set forth in SEQ ID NO: 1, but rather any combination of nucleotides present in a sequence. This occurs because the pending claims encompass a nucleotide sequence that is 99% identical to the sequence set forth in SEQ ID NO: 1 however this sequence further comprises 1 to 100 amino acid C- and N-terminal deletions relative to the full-length sequence of SEQ ID NO: 1. Since this nucleotide sequence is relative to any of the nucleotides set forth in SEQ ID NO: 1, and still is required to have a functional property, the skilled artisan could not rely upon the disclosure in the specification that would sufficiently describe that Applicant was in possession of the nucleic acid of claim 1 at the time of filing. While the structure and function of the GEM protein and nucleotide sequence is known, the specification has not described any other structural characteristics of a nucleic acid that has reduced affinity for calmodulin functional characteristics other than the full-length nucleotide sequence set forth in SEQ ID NO: 1.

Applicants' attention is directed to the decision in In re Wallach, 71, USPQ2d 1939 (Fed. Circ. 2004) wherein is stated:

“As Appellants point out, we have recognized that the written description requirement can in some cases be satisfied by functional description. *See, e.g.*, *Enzo*, 296 F.3d at 1324 (“It is not correct, however, that all functional descriptions of genetic material fail to meet the written description requirement.”). Nonetheless, such functional description can be sufficient only if there is also a structure-function relationship known to those of ordinary skill in the art. As we explained above, such a well-known relationship exists between a nucleic acid molecule's structure and its function in encoding a particular amino acid sequence: Given the amino acid sequence, one can determine the chemical structure of all nucleic acid molecules that can serve the function of encoding that sequence. Without that sequence, however, or with only a partial sequence, those structures cannot be determined and the written description requirement is consequently not met. As we explained in *Enzo*, the *Guidelines for Examination of Patent Applications under the 35 U.S.C. §112, ¶ 1, "Written Description" Requirement*, 66 Fed. Reg. 1099 (Jan. 5, 2001) ("*Guidelines*"), state that

> the written description requirement can be met by "show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics … *i.e.*, complete or partial structure, other physical and/or chemical properties, *functional characteristics when coupled with a known or disclosed correlation between function and structure*, or some combination of such characteristics." *Guidelines*, 66 Fed. Reg. at 1106 (emphasis added).

Enzo, 296 F.3d at 1324-25 (emphasis added)."

In conclusion, this limited information is not deemed sufficient to reasonably convey to one skilled in the art that applicant is in possession of any protein that will modulate calcium channel activity.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Montanari whose telephone number is (571)272-3108. The examiner can normally be reached on M-Tr 8-6.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 1-571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

David A. Montanari
AU 1632

/Peter Paras, Jr./
Supervisory Patent Examiner, Art Unit 1632